#18 12/26/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Livak et al.

Serial No.: 09/627,753

Filed: July 28, 2000

For: **Hybridization Assay Using Self-Quenching Fluorescence Probe**

Group Art Unit: 1637

Examiner: J. Riley

CERTIFICATE OF EXPRESS MAILING

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RESPONSE UNDER 37 CFR 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

With reference to the Office action mailed Feb. 4, 2002, reconsideration of the application is respectfully requested. Enclosed herewith are a Request for Continued Examination and a Petition for 3-Month Extension of Time (in connection with the Notice of Appeal submitted July 5, 2002). Claims 39-40 are pending.

In the Office action mailed Feb. 4, 2002, the Examiner reiterated, without elaboration, the prior rejections set forth in the prior Office action mailed June 22, 2001. This position is not understood.

I. Rejection Under 35 U.S.C. 103(a)

As noted in Applicant's response submitted on December 26, 2002, the obviousness rejection over Heller et al. (EP 229943) in view of Urdea et al. (US 4,775,619) is believed to be improper because the cited references do not support a prima facie case of obviousness.

Independent claim 39 recites a method for detecting nucleic acid target sequences wherein a sample is contacted with an oligonucleotide probe attached to a solid support under

conditions favorable for hybridization. The oligonucleotide probe includes a fluorescent reporter molecule and a quencher molecule capable of quenching the fluorescence of said reporter molecule. The probe exists in at least one single-stranded conformation when unhybridized to target where the quencher molecule quenches the fluorescence of the reporter molecule, and at least one conformation when hybridized to the target where the fluorescence intensity of the reporter molecule is unquenched, such that the ratio of the fluorescence intensities of the reporter molecule to the quencher molecule when the probe is hybridized to the target is greater than the ratio when the probe is single-stranded. The fluorescence of the reporter molecule is then monitored, wherein an increase in the fluorescence intensity of the reporter molecule indicates the presence of the target sequence.

The PTO has the burden of establishing *prima facie* obviousness, and can meet this burden "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references" In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Heller teaches fluorescent probes for use in hybridization. In the "single probe embodiment", a DNA probe containing a donor and an acceptor separated by 2 to 7 nucleotide bases is contacted with a target polynucleotide (e.g., see page 7 starting at the second full paragraph through page 8 line 12, and Fig. 1). In the "dual probe embodiment", two probes are hybridized adjacently to each other on a target sequence so that a donor fluorophore on one of the probes is 2 to 7 bases from an acceptor dye on the other probe (Idem, and Fig. 2). After probe hybridization, fluorescent signal is measured from the emitted light from the acceptor dyea

Heller also teaches use of a support wherein the target is immobilized on a support for hybridization with the probe(s) (e.g., see page 14). There is no teaching or suggestion of an oligonucleotide probe attached to a solid support, wherein the probe includes a fluorescent reporter molecule and a quencher molecule as recited in claim 39.

The deficiencies of Heller are not overcome by Urdea, which was cited merely for describing assays that utilize solid supports.

Only in hindsight could the present claims have been deemed to be obvious, as there appears to be no teaching or suggestion of the present invention, wherein a probe as recited in claims 39-40 is contacted with a nucleic acid sample and the reporter is monitored, wherein an increase in the fluorescence intensity of the reporter molecule indicates the presence of the target sequence. In

the absence of motivation in the cited art to combine the teachings thereof to arrive at the present invention, the claims cannot be considered obvious. Withdrawal of the rejection is therefore respectfully requested.

II. Obviousness Type Double Patenting Rejection

Claims 39-40 were rejected as allegedly being unpatentable over claims in U.S. 5,876,930 and 6,030,787. It is requested that this rejection be held in abeyance until allowable subject matter is indicated by the Examiner.

III. Fee Authorization

Should any extension of time and/or fee be necessary for timely submission of this paper, such extension of time is hereby requested, and the Commissioner is hereby authorized to charge **Deposit Account No. 01-2213 (Order No. 4264C5)**. Any deficiency or overpayment should be charged or credited to this deposit account.

Respectfully submitted,

Date: Dec 5, 2002

Vincent M. Powers
Reg. No. 36,246
Attorney for Applicants

CORRESPONDENCE ADDRESS
Customer Number: 22896
APPLIED BIOSYSTEMS
850 Lincoln Centre Drive
Foster City, California 94404
TEL: 650-638-6492
FAX: 650-638-6677